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(54) **Absorbable composite materials for use in the treatment of periodontal disease**

Absorbierbare Verbundstoffe zur Verwendung in der Behandlung von Wurzelhauterkrankungen des Zahns

Matériaux composites absorbables pour utilisation pour le traitement des périodontoses

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## Description

**[0001]** The present invention relates to the use of absorbable composite materials in the form of a strip or film for the preparation of medicaments for use in the treatment of periodontal disease.

**[0002]** "Periodontal disease" is the term commonly used to describe inflammatory disease of the periodontium (tooth-surrounding tissue). It is a widespread disease in mammals, particularly humans, and chronic inflammatory periodontal disease (CIPD) is the major cause of tooth loss in adults.

**[0003]** CIPD results from the accumulation of dental plaque in the gingival crevice, i.e. the gap between the gingiva and the tooth which is normally about 1mm deep. The epithelial attachment to the tooth forms a barrier between the external environment in the mouth and the tooth-supporting tissues. An increase in dental plaque leads to gingivitis, and successive inflammatory reactions cause the progressive erosion of the tooth-supporting tissues which are the collagenous fibres and the bone socket in which the tooth sits. This erosion is manifested by an enlargement of the gingival crevice which may become many millimeters deep.

**[0004]** Treatment of CIPD has traditionally been focused on the destruction or removal of the bacterial plaque whose accumulation perpetuates the disease. This is commonly practised by one or both of two approaches: surgical intervention and non-surgical treatment. The surgical approach comprises reflecting the gingival tissue to expose the tooth root in order that mechanical removal of the plaque may be accomplished directly, by e.g. scraping, the use of ultrasonics or laser methods. Following this debridement, the gingival tissue is sutured back in position. This procedure is time-consuming, painful and requires substantial specialist resources.

**[0005]** The non-surgical approach usually comprises limited mechanical debridement (e.g. scraping and irrigation) via the entrance to the periodontal pocket, followed by antibacterial chemotherapy. This chemotherapy may take the form of systemic antibiotics, of which tetracyclines and imidazoles are commonly used, or the localised application of the antibacterial agent via the periodontal pocket. In addition to antibiotics, antiseptics such as chlorhexidine can be introduced to the periodontal tissues in this manner. Advantages of the local administration of antibacterial agents are the relatively higher concentrations achievable in the periodontal tissues, compared with those obtained by systemic therapy, and also a decreased risk of producing bacterial resistance to the agent. Furthermore, the use of the non-surgical approach is less traumatic for the patient and is less demanding on professional resources.

**[0006]** For these reasons, the treatment of CIPD by non-surgical intervention and locally-applied antimicrobial agents is gaining popularity. However, there is a major problem with the delivery of the antimicrobial agent to the tissues, and more particularly with maintaining sufficiently high concentrations to be therapeutically efficaceous in a manner which is practical and acceptable to the patient. The introduction of the agent into the periodontal pocket by the injection of a solution (e.g. by syringe or pulsed-jet irrigation, see Newman, J. Clin Periodontal, 1986, 13: 965-974) often results in rapid loss of the agent from the site, either by exudation into the oral cavity or by rapid diffusion and dilution in the surrounding tissues, thereby requiring repeated applications which are impractical. This has led to the need for an appropriate system or 'vehicle' for the sustained delivery of the therapeutic agent in order to maintain pharmacologically-effective concentrations for an acceptably long period following a single administration. Considerable efforts have been made by many in the field to devise such a carrier with the requisite degree of bioacceptibility, mechanical characteristics, retention time and controlled release properties.

**[0007]** For example, US-A-4685883 (Jernberg) describes a method of local delivery of chemotherapeutic agents to the periodontal pocket by inserting into the periodontal pocket time-release microspheres comprising the chemotherapeutic agent dispersed in a biodegradable solid. A drawback of this method is that the time-release microspheres tend to leak out of the periodontal pocket.

**[0008]** US-A-4892736 (Goodson) describes a system for delivering a chemotherapeutic agent to the site of a periodontal infection which comprises a biodegradable fibre such as an ethylene vinyl acetate (EVA) copolymer fibre containing the chemotherapeutic agent. A length of the fibre is inserted into the periodontal pocket, and is retained there by a retaining means such as an elastic band. A drawback of this system is that the retaining means tends to cause irritation of the infected gum tissue.

**[0009]** US-A-4933182 (Higashi *et al.*) describes a controlled-release pharmaceutical composition in the form of a gel, sheet, film or bar to be inserted into a periodontal pocket. The composition comprises a chemotherapeutic agent dispersed in a two-phase carrier consisting of: (a) a continuous phase of a water-soluble polymer, and (b) a discontinuous phase of solid particles that are soluble in the pH range 4.0 to 6.0

**[0010]** US-A-4789662 (Thomas-Lerquin *et al.*) describes a method of treating periodontal disease by inserting into the periodontal pocket a collagen film having a chemotherapeutic agent dispersed therein. The collagen film biodegrades slowly in the periodontal pocket to release the chemotherapeutic agent.

**[0011]** US-A-4906670 (Higashi *et al.*) describes a medicated film for insertion into the periodontal pocket to provide sustained release of a chemotherapeutic agent. The film consists of the chemotherapeutic agent dispersed in glutaraldehyde cross-linked succinylated atelocollagen gel in a 1 to 9 ratio with hydroxypropylcellulose.

**[0012]** EP-A-0388220 (Yissum) describes periodontal implants consisting of an effective amount of chlorhexidine gluconate in a water insoluble protein matrix. The protein preferably comprises cross-linked gelatin, albumin, an enzyme or fibrinogen. The implant may also contain a plasticiser such as glycerol.

**[0013]** The above-described medicated films for the treatment of periodontal disease provide the advantages of ease of insertion into the periodontal pocket, followed by slow release of a chemotherapeutic agent over a period of time. The films themselves may be formed of biodegradable materials that are compatible with the periodontal pocket and do not interfere with healing.

**[0014]** However, up until now no completely satisfactory slow-release film for the treatment of periodontal disease has been developed. This is because of the following conflicting requirements for the properties of the film.

**[0015]** The first requirement is that the film should be stiff when dry so that it is easy for the dental practitioner to handle and easy to insert deep into the periodontal pocket.

**[0016]** The second requirement is that the film should be soft and conformable in use, i.e. after it has been inserted into the periodontal pocket. This is to avoid irritation of the periodontal pocket by the inserted film.

**[0017]** The third requirement is that the film should be retained in the periodontal pocket for extended periods without falling out either spontaneously or as a result of normal oral hygiene measures, such as flossing or brushing, which-are required to maintain gingival health.

**[0018]** The fourth requirement is that the film should release the chemotherapeutic agent at a slow, controllable rate over an extended period. Preferably, the film should remain effective for up to 30 days *in situ,* since inserting a replacement film is inevitably somewhat traumatic to the periodontal pocket.

**[0019]** EP-A-0194192 (Ethnor) describes a bioabsorbable composite material for use as a graft or prosthesis in surgery. The material comprises a woven or knitted mesh of resorbable fibres (such as fibres of a copolymer of lactic acid and glycolic acid) embedded in a continuous film of collagen. The collagen film renders the composite watertight, e.g. for use as an arterial graft. The underlying fibrous structure provides sufficient mechanical strength for the composite to hold sutures. However, there is no suggestion that these composites could be used for controlled release of chemotherapeutic agents.

**[0020]** It has now been found that slow-release chemotherapeutic films that are outstandingly suitable for the treatment of periodontal disease may be made by dispersing chemotherapeutic agents in composite materials similar to those disclosed in EP-A-0194192.

**[0021]** EP-A-0567234, which forms part of the state of the art by virtue of Article 54(3) EPC, describes biopolymer composites comprising oleaginous material dispersed in a solid collagen matrix. The composites may be reinforced by incorporating a biodegradable or non-biodegradable mesh. The composites may incorporate active agents such as antiseptics or antibiotics. The composites are intended for use as topical wound dressings.

**[0022]** The present invention provides use of a composite material comprising a collagen matrix reinforced with a layer of a bioabsorbable polymer and having a chemotherapeutic agent dispersed therein for the preparation of a medicament for use in the treatment of periodontal disease wherein the composite material is substantially free of oleaginous material dispersed in the collagen matrix.

**[0023]** Preferably, the collagen is reinforced by a layer of a synthetic bioabsorbable material or a modified cellulose or an alginate. The layer may be in the form of a continuous or perforated sheet or web. Preferably, the layer is a mesh of woven, nonwoven or knitted fibres. Preferred bioabsorbable polymers include suture materials such as copolymers of lactic acid and glycolic acid, or oxidised regenerated cellulose. A particularly preferred synthetic bioabsorbable polymer is the polylactic/polyglycolic acid copolymer sold under the Registered Trade Mark VICRYL. Also particularly preferred is the oxidised regenerated cellulose mesh sold under the Registered Trade Mark SURGICEL.

**[0024]** The collagen matrix may comprise insoluble Type I and/or Type III collagen fibres. Alternatively or additionally the collagen matrix may comprise soluble collagen, such as gelatin or atelocollagen or acid soluble collagen, or even collagen fibres reconstituted from these soluble collagens. The collagen may be obtained from any animal, fish or avian source, but is preferably obtained from bovine corium.

**[0025]** The relative amounts of collagen and bioabsorbable polymer mesh in the composite materials used in the present invention may vary widely, depending on the physical characteristics and the rate of dissolution of the composite material that are required. The composite preferably comprises 20% to 60% by weight of collagen.

**[0026]** The chemotherapeutic agent may comprise an antibiotic such as tetracycline, neomycin or metranidazole. Alternatively or additionally the chemotherapeutic agent may comprise a local anaesthetic such as benzocaine or lidocaine. Alternatively or additionally the chemotherapeutic agent may comprise an antiseptic such as iodine, chlorhexidine or a phenolic antiseptic. Alternatively or additionally the chemotherapeutic agent may comprise an anti-inflammatory such as hydrocortisone or indomethacin.

**[0027]** The chemotherapeutic agent is preferably dispersed in the collagen matrix, but it may alternatively or additionally be dispersed in the material of the reinforcing layer. Different chemotherapeutic agents may be dispersed in the collagen matrix and the reinforcing layer so as to achieve phasic release of the different chemotherapeutic agents.

**[0028]** The chemotherapeutic agent is preferably present in an amount of 0.01% to 10% by weight based on the weight of the composite material. More preferably, the chemotherapeutic agent is present in an amount of from 0.1% to 5% by weight based on the weight of the composite material.

**[0029]** The collagen matrix preferably also contains up to 5% by weight, based on the weight of the composite, of an anionic polysaccharide such as an alginate or a glycosaminoglycan, for example hyaluronic acid or chondroitin sulphate. These anionic polysaccharides have soothing and humectant properties and are believed to assist wound healing.

**[0030]** The collagen matrix preferably also contains up to 20% by weight based on the weight of the composite of a plasticiser. Preferred plasticisers include the polyhydric alcohols such as glycerol.

**[0031]** The composite materials used in the present invention are preferably made as follows. First, a slurry of insoluble collagen and/or a solution of soluble collagen in a dilute aqueous acid is prepared. Then other ingredients of the collagen matrix such as the chemotherapeutic agent, the anionic polymer and the plasticiser are added to the slurry and the slurry is homogenised.

**[0032]** The homogenised collagen slurry is then poured over the reinforcing layer, which has been laid out in a flat-bottomed tray. Once the reinforcing layer is covered with the slurry, the water is removed by air-drying or freeze-drying, to leave a sheet of the composite material.

**[0033]** The reinforcing layer is preferably a layer of commercially available VICRYL or SURGICEL mesh fabric.

**[0034]** The composite materials used in the present invention are preferably formed as flat sheets having a preferred thickness of 0.5-2.0 mm. The sheets are cut into strips, typically measuring 1-10 mm by 1-10 mm, and these strips are then inserted into the periodontal pocket.

**[0035]** Some embodiments of the reinforced films used in the present invention, and their method of manufacture, will now be described further by way of example.

Example 1

**[0036]** A composite material comprising an insoluble collagen matrix having chlorhexidine and calcium alginate dispersed therein is prepared as follows:-

**[0037]** Fibrous collagen, prewashed to remove the majority of non-collagenous components as described in US-A-4614794 or US-A-4320201 is suspended in clean deionised pyrogen-free water and homogenised to a fine fibrous suspension by passage through a homogenising system, such as described in US-A-4320201. The collagen suspension is then acidified with 0.05 M acetic acid to form a swollen fibrous dispersion.

**[0038]** A homogenised suspension of calcium alginate fibres is mixed with a solution of chlorhexidine digluconate in a ratio of 1:1 (w/w) and then blended with the suspension of collagen fibres in 0.05 m acetic acid. The mixture is degassed and poured onto a sheet of Vicryl polylactide/polyglycolide polymer (Registered Trade Mark) and dried under a stream of filtered air at room temperature. The dried composite material is cut into 10 mm X 2 mm strips.

Example 2

**[0039]** A composite material comprising a soluble collagen matrix having chlorhexidine and calcium alginate dispersed therein is prepared as follows:

**[0040]** Soluble atelopeptide collagen is obtained from limed or unlimed bovine corium by extraction with pepsin. Finely diced, pulped or minced hide is added to 0.05 M acetic acid and agitated for 24 hours with pepsin (50:1 collagen:pepsin, w/w) at 20°C. Insoluble residue is removed by centrifugation and the pepsin in the supernatant deactivated by raising the pH to 8.0 with ammonium hydroxide. The solution of atelocollagen is reacidified with acetic acid, precipitated with NaCl (5%, w/v) centrifuged, and redissolved in 0.05 M acetic acid.

**[0041]** A homogenised suspension of calcium alginate fibres is mixed with a solution of chlorhexidine gluconate in a ratio of 1:1 (w/v) and then blended with the solution of atelocollagen in 0.05 M acetic acid. The mixture is degassed and poured onto a layer of SURGICEL (Registered Trade Mark) oxidised regenerated cellulose mesh and dried under a stream of filtered air at room temperature.

Example 3

**[0042]** A composite material comprising a cross-linked collagen matrix having chlorhexidine and calcium alginate dispersed therein is prepared as described in Example 2 above, with the additional step of cross-linking carried out on the collagen-chlorhexidine-alginate solution using carbodiimide prior to degassing and pouring onto a vicryl mesh.

Example 4

**[0043]** A composite material wherein the collagen matrix is further reinfored by the addition of fibres of oxidised cellulose is prepared as in Example 1 above, with the additional step of adding finely milled fibres of oxised cellulose (obtained by carding SURGICEL fabric) to the collagen-chlorhexidine slurry prior to degassing and pouring the slurry onto a VICRYL mesh layer.

Example 5

**[0044]** A further composite material wherein the collagen matrix is further reinforced by the presence of oxidised regenerated cellulose is prepared by, first, dis-

solving oxidised cellulose fibres in 0.01 M ammonium hydroxide, followed by adding this solution to a solution of atelocollagen in 0.05 M acetic acid prepared as in Example 2. The resulting precipitated material is homogenised to form a slurry, chlorhexidine is added to the slurry as described in Examples 1 and 2, and the slurry is then degassed. The degassed slurry is poured onto a sheet of VICRYL mesh and dried under flowing filtered air at room temperature.

**[0045]** The composites described above have been found to be exceptionally suitable for the treatment of periodontal disease. The composite materials are easy to handle and to cut into any desired shape. Strips of the materials are sufficiently rigid to be inserted deep into the periodontal pocket. Once inserted, the materials absorb fluid within minutes to become soft, conformable and comfortable while maintaining good structural integrity. The absorbed fluid causes the materials to swell so that they fill the periodontal pocket and are held firmly in place by the swelling pressure, without the need for any additional retaining means, for up to 30 days.

**[0046]** This provides for sustained release of the chemotherapeutic agents over an extended period without the need to insert a fresh strip every few days. The composite materials are completely biocompatible and absorbable.

### Claims

1. Use of a composite material comprising a collagen matrix reinforced with a layer of a bioabsorbable polymer and having a chemotherapeutic agent dispersed therein for the preparation of a medicament for use in the treatment of periodontal disease, wherein the composite material is substantially free of oleaginous material dispersed in said collagen matrix.

2. Use of a composite material according to claim 1 wherein the collagen matrix comprises insoluble collagen.

3. Use of a composite material according to claim 1 or 2 wherein the layer of a bioabsorbable polymer comprises a woven, nonwoven or knitted mesh of the bioabsorbable polymer.

4. Use of a composite material according to any preceding claim wherein the bioabsorbable polymer is a synthetic bioabsorbable polymer or a modified cellulose.

5. Use of a composite material according to claim 4 wherein the bioabsorbable polymer comprises a copolymer of lactic acid and glycolic acid or oxidised regenerated cellulose.

6. Use of a composite material according to any preceding claim wherein the chemotherapeutic agent comprises an antibiotic, an anaesthetic, an antiseptic or an anti-inflammatory.

7. Use of a composite material according to any preceding claim wherein the chemotherapeutic agent is present in an amount of 0.01% to 10% by weight, based on the weight of the composite material.

8. Use of a composite material according to claim 7 wherein the chemotherapeutic agent is present in an amount of from 0.1% to 5% by weight, based on the weight of the composite material.

9. Use of a composite material according to any preceding claim wherein the matrix further comprises an anionic bioabsorbable polymer in an amount up to 10% by weight, based on the weight of the composite material.

10. Use of a composite material according to any preceding claim wherein the matrix farther comprises a plasticiser.

11. Use of a composite material according to claim 10, wherein the plasticiser is a polyhydric alcohol.

12. Use of a composite material according to any preceding claim in the form of a sheet or strip having a thickness of from 0.5 to 2.0 mm.

### Patentansprüche

1. Verwendung eines Verbundstoffes, umfassend eine Kollagenmatrix, die mit einer Schicht eines bioabsorbierbaren Polymers verstärkt ist, und die ein chemotherapeutisches Agens aufweist, das darin dispergiert ist, für die Herstellung eines Medikaments zur Verwendung in der Behandlung von Wurzelhauterkrankungen des Zahns, **dadurch gekennzeichnet, daß** der Verbundstoff im wesentlichen frei von ölartigem Material ist, das in der Kollagenmatrix dispergiert ist.

2. Verwendung eines Verbundstoffes nach Anspruch 1, **dadurch gekennzeichnet, daß** die Kollagenmatrix unlösliches Kollagen umfaßt.

3. Verwendung eines Verbundstoffes nach Anspruch 1 oder 2, **dadurch gekennzeichnet, daß** die Schicht eines bioabsorbierbaren Polymers ein gewebtes, nicht-gewebtes oder gestricktes Gittergewebe des bioabsorbierbaren Polymers umfaßt.

4. Verwendung eines Verbundstoffes nach einem der vorangehenden Ansprüche, **dadurch gekenn-**

**zeichn t, daß**
das bioabsorbierbare Polymer ein synthetisches bioabsorbierbares Polymer oder eine modifizierte Zellulose ist.

5. Verwendung eines Verbundstoffes nach Anspruch 4, **dadurch gekennzeichnet, daß** das bioabsorbierbare Polymer ein Copolymer aus Milchsäure und Glycolsäure oder oxidierte, regenerierte Zellulose umfaßt.

6. Verwendung eines Verbundstoffes nach einem der vorangehenden Ansprüche, **dadurch gekennzeichnet, daß**
das chemotherapeutische Agens ein Antibiotikum, ein Anaesthetikum, ein Antiseptikum oder ein entzündungshemmendes Mittel umfaßt.

7. Verwendung eines Verbundstoffes nach einem der vorangehenden Ansprüche, **dadurch gekennzeichnet, daß**
das chemotherapeutische Agens in einer Menge von 0,01% bis 10 Gew.-%, basierend auf dem Gewicht des Verbundstoffes, vorliegt.

8. Verwendung eines Verbundstoffes nach Anspruch 7, **dadurch gekennzeichnet, daß** das chemotherapeutische Agens in einer Menge von 0,1 bis 5 Gew.-%, basierend auf dem Gewicht des Verbundstoffes, vorliegt.

9. Verwendung eines Verbundstoffes nach einem der vorangehenden Ansprüche, **dadurch gekennzeichnet, daß**
die Matrix weiter ein anionisches, bioabsorbierbares Polymer in einer Menge von bis zu 10 Gew.-%, basierend auf dem Gewicht des Verbundstoffes, umfaßt.

10. Verwendung eines Verbundstoffes nach einem der vorangehenden Ansprüche, **dadurch gekennzeichnet, daß**
die Matrix weiter einen Weichmacher umfaßt.

11. Verwendung eines Verbundstoffes nach Anspruch 10, **dadurch gekennzeichnet, daß** der Weichmacher ein mehrwertiger Alkohol ist.

12. Verwendung eines Verbundstoffes nach einem der vorangehenden Ansprüche, in der Form eines Blattes oder Streifens mit einer Dicke von 0,5 bis 2,0 mm.

**Revendications**

1. Utilisation d'un matériau composite comprenant une matrice de collagène renforcée par une couche d'un polymère bioabsorbable et possédant un agent chimiothérapeutique dispersé dans cette couche pour la préparation d'un médicament destiné à être utilisé pour le traitement d'une périodontite, le matériau composite étant essentiellement exempt de matériau oléagineux dispersé dans ladite matrice de collagène.

2. Utilisation d'un matériau composite selon la revendication 1, dans laquelle la matrice de collagène comprend du collagène insoluble.

3. Utilisation d'un matériau composite selon la revendication 1 ou 2, dans laquelle la couche d'un polymère bioabsorbable comprend une structure maillée tissée, non tissée ou tricotée du polymère bioabsorbable.

4. Utilisation d'un matériau composite selon l'une quelconque des revendications précédentes, dans laquelle le polymère bioabsorbable est un polymère bioabsorbable synthétique ou une cellulose modifiée.

5. Utilisation d'un matériau composite selon la revendication 4, dans laquelle le polymère bioabsorbable comprend un copolymère d'acide lactique et d'acide glycolique ou de cellulose oxydé et régénéré.

6. Utilisation d'un matériau composite selon l'une quelconque des revendications précédentes, dans laquelle l'agent chimiothérapeutique comprend un antibiotique, un anesthésique, un antiseptique ou un anti-inflammatoire.

7. Utilisation d'un matériau composite selon l'une quelconque des revendications précédentes, dans laquelle l'agent chimiothérapeutique est présent en une quantité comprise entre 0,01 et 10 % en poids, sur la base du poids du matériau composite.

8. Utilisation d'un matériau composite selon la revendication 7, dans laquelle l'agent chimiothérapeutique est présent en une quantité comprise entre 0,1 et 5 % en poids, sur la base du poids du matériau composite.

9. Utilisation d'un matériau composite selon l'une quelconque des revendications précédentes, dans laquelle la matrice comprend en outre un polymère anionique bioabsorbable en une quantité atteignant jusqu'à 10 % en poids, sur la base du poids du matériau composite.

10. Utilisation d'un matériau composite selon l'une quelconque des revendications précédentes, dans laquelle la matrice comprend en outre un plastifiant.

11. Utilisation d'un matériau composite selon la revendication 10, dans laquelle le plastifiant est un alcool polyhydrique.

12. Utilisation d'un matériau composite selon l'une quelconque des revendications précédentes sous la forme d'une feuille ou d'une bande possédant une épaisseur comprise entre 0,5 et 2,0 mm.